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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,046	04/30/2001	Peter Hevezi	A-69199-1/DJB/JJD	5223

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	14

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,046	HEVEZI ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-6, 8-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claim 44, which is related to claims 7, 39-43 and is not new matter.

Accordingly, claims 7, 39-44 are examined in the instant application, drawn to a method for detecting prostate cancer, comprising determining the mRNA level of a gene encoding PAA3 protein.

This application contains claim drawn to an invention nonelected with traverse in Paper No.10 A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

OBJECTION

1. Claim 7 remains objected because part of claim 7 is drawn to non-elected invention.

Applicant argues that the claim is explicitely drawn to a method for diagnosis of prostate or breast cancer, comprising determining the expression level of a gene encoding PAA3 protein, not to the determination of the PAA3 protein level expression.

Objection remains, because expression level of a gene encompasses both protein and mRNA expression level of a gene.

2. Claim 7, as amended, is objected to, because claim 7 recites a first prostate tissue from a first individual, without reciting any subsequent individual. It is not clear the first individual is first as compared to what.

3. Claim 7 is objected to for the use of the language "higher", which does not set forth the metes and bound of the patent protection desired. This rejection could be obviated by amending the claim for example to recited "an increased level".

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 7, 39-43 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a method for detecting prostate cancer, for reasons already of record in paper No:11. New claim 44 is rejected for the same reasons already of record.

Applicant argues that the claimed method possess the sensitivity and specificity to identify tumor markers of prostate cancer, using at least 90 control samples, and 54 different primary prostate tumors. The results verify that the methods in US Application Nos: 09/733288 and 09/687576, of which this application claims priority to, that the gene encoding PAA3 is overexpressed in prostate cancer tissues as compared to hundreds of other genes screened on the biochip array.

Applicant recites Lockhart et al, 1996, asserting that the methods of transcribing cRNAs for amplification and analysis of gene expression is known in the art. Applicant further asserts that the manufacturers of microarrays have long recommended this technique for gene expression analysis.

Applicant asserts that the '002 patent recited by the Examiner merely discloses that cRNA is inefficient because it does not amplify as readily as PCR and therefore requires a larger sample of mRNA as compared to PCR assays. The instant cRNA methods and expression assays are reliable, given the large milligram amounts of starting material.

Applicant further asserts that the instant invention uses T7 polymerase, which is very efficient, and does not require additional enhancer for high transcriptional rates, without compromising fidelity of the transcript. Applicant asserts that the methods disclosed in Lewin, recited by the Examiner, relate to RNA polymerase II, a promoter that is far less efficient than the T7 phage promoter.

Applicant asserts that quality control and quantification of starting mRNA or cRNA is done at various stages of the assays, and that more importantly, marker genes are identified through their increased expression levels as compared to other hundreds of genes immobilized on oligonucleotide hybridization microarray. Applicant asserts that the relative expression of many genes within a given tissue sample as compared to normal tissue that is relevant.

The recitation of the reference by Lockhart et al, 1996 is acknowledged and has been entered.

Applicant's arguments have been considered but are found not to be persuasive for the following reasons:

Contrary to Applicant arguments, there is no disclosure in the specification of quantification of starting mRNA or cRNA. Although the large milligram amounts of

starting material is used, this does not indicate that the cRNAs produced are representative of the original mRNAs. It is not clear that the genes expressed as cRNAs bound to the oligonucleotides arrays are representative of the original mRNAs. However, similar to the requirement for cDNA libraries, representative cRNAs are necessary to ensure that the detected differential expression is not due to artifact of the analytical system. There is however inadequate disclosure in the specification of the total original mRNAs represented by cRNAs that are used for hybridization to oligonucleotide array, in view that there are as many as $1\text{-}3x10^5$ different mRNA molecules, each of which varies in abundance or frequency within a given cell (US 6,271,002B1, column 1, lines 60-63, of record). There is inadequate disclosure of whether the disclosed cRNAs are not multiple copies of certain original mRNAs and not representative of certain oher original mRNAs. Moreover, there is inadequate disclosure of the number of cRNAs that could be accommodated by the oligonucleotide arrays such that the number of cRNAs are representative of the total original mRNAs.

Thus the fact that SEQ ID NO:1 is not expressed in one set of cRNAs bound to the oligonucleotide arrays or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is overexpressed in the prostate cancer tissue represented in cRNAs bound to the oligonucleotide arrays.

Moreover, examination of different applications is separate, and thus whether the methods of US Application Nos: 09/733288 and 09/687576 are enabled or not are not germane to the instant application.

Further, although the methods of transcribing cRNAs for amplification and analysis of gene expression is known in the art, this does not exclude the issue that the claimed invention does not seem to disclose whether the genes expressed as cRNAs bound to the oligonucleotides arrays are representative of the original mRNAs. Further, Lockhart et al, 1996, teach that "representative" cDNA libraries were used in the experiments (p.1677, first column, line 6) or the entire mRNA population is amplified by 20 to 250 fold in an apparently unbiased fashion (p.1678, first column, second paragraph) for use in the experiment. Lockhart et al, 1996 further teach that to determine the range of concentration over which hybridization signals could be used for direct quantitation of RNA levels, ten cytokines were spiked or labeled, and a frequency of 1:300,000 is that of an mRNA present at about 1 to 3 copies per cell (p. 1677, first column, first paragraph). Based on the disclosure in the specification, it is not clear however how abundant the mRNAs of SEQ ID NO:1 are in a prostate cell, and which frequency of SEQ ID NO:1 in a prostate cell was determined such that it is represented in the cRNAs, nor is it clear what the total number of cRNAs are used in the arrays for the assay such that it is representative of total prostate cell mRNAs.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 7, 40-43 remain rejected under 35 USC 112, first paragraph for lack of a clear written description for reasons already set forth in paper No:11. New claim 44 is rejected for the same reasons already of record.

The amended claims 7, 40-43 and new claim 44 are now drawn to a method for detecting prostate cancer, comprising determining the expression of a "gene encoding SEQ ID NO:2", wherein said expression is measured using a nucleic acid probe "complementary" to SEQ ID NO:1.

Applicant asserts that claims 7, 40-43 have been amended and thus the written description rejection has been obviated.

Applicant's arguments in paper No:12 have been considered but are found not to be persuasive for the following reasons:

It is noted that a "gene" encompasses genomic DNA sequence. The specification however fails to describe the 5' and 3' regulatory regions, the structure of which are not conventional in the art, as taught by Harris et al, Ahn et al and Cawthon et al, all of record.

Further, it is noted that a complement could be a partial or full length complement, wherein a partial complement of a sequence could share with the sequence only a few complementary nucleotides. Thus a probe that is complementary to SEQ ID NO:1 encompasses unrelated sequences with unknown structure.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 40-42 remain rejected under 112, first paragraph, for lack of enablement for a probe "complementary" to SEQ ID NO:1 for reasons already of record in paper No:11.

Applicant asserts that claims 40-42 have been amended and thus the rejection has been obviated.

Applicant's arguments in paper No:12 have been considered but are found not to be persuasive for the following reasons:

It is noted that a complement could be a partial or full length complement, wherein a partial complement of a sequence could share with the sequence only a few complementary nucleotides. The a probe that is complementary to SEQ ID NO:1 encompasses unrelated sequences with unknown structure.

REJECTION UNDER 35 USC 102(e)

Claims 7, 39-42 remain rejected under 35 USC 102(e) as being anticipated by PCT/US 01/05171, for reasons already of record in paper No:11.

Applicant argues that the sequence taught by PCT/US 01/05171 is not identical to SEQ ID NO:1 of the instant invention. Applicant further argues that one would not expect that method taught by PCT/US 01/05171 would detect the claimed SEQ ID NO:1, because one would assume that a practitioner of the disclosed invention would design a probe specific for the sequence of interest.

Applicant's arguments in paper No:12 have been considered but are found not to be persuasive for the following reasons:

It is noted that the probe as disclosed in claim 40 is not specific for SEQ ID NO:1, because a complement could be a partial or full length complement, wherein a partial

complement of a sequence could share with the sequence only a few complementary nucleotides.

Thus one would expect that the method taught by PCT/US 01/05171 would detect the claimed SEQ ID NO:1, which ahs 97% similarity to SEQ ID NO:1, from nucleotide 1664 to nucleotide 4363.

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

October 30, 2003